FINAL REPORT
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NEUROBIOLOGY OF LEARNING AND MEMORY: MODULATION AND MECHANISMS

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MODULATION OF MEMORY STORAGE

It has been known for many years that the retention of newly-acquired information can be modulated by a variety of treatments if the treatments are administered shortly after training. Such findings suggest that the processes underlying memory storage may be modulated by endogenous systems activated by training experiences. Our research has examined the possibility that hormonal systems activated by training may serve this role. Our recent work has focussed on the central mechanisms underlying the effects, on memory modulation, of treatments affecting adrenergic and opiate receptor systems. The findings of our recent research supported by this contract strongly suggest that treatments affecting adrenergic receptor systems as well as opiate receptor systems modulate memory through influences involving noradrenergic receptors in the amygdala.

Keywords: Epinephrine, Pharmacological antagonists, Nerve transmission, Nerve cells, Cerebral cortex, Learning, Behavior

Epinephrine Effects on Memory

Numerous studies have reported that, in rats and mice, systemic administration of the adrenal medullary hormone epinephrine immediately following a training session alters subsequent retention of the response. Retention is enhanced by low doses and impaired by high doses. Since epinephrine is known to be released from the adrenal medulla by the kind of aversive stimulation typically used in animal memory experiments, the findings have been interpreted as supporting the view that endogenously-released epinephrine has effects which serve to modulate the storage of recently acquired information. If it is assumed that epinephrine effects on memory are due to a general modulating effect on memory storage, then the effects should not be restricted to any particular learning task. There is clear evidence that posttraining administration of epinephrine affects retention of both active and inhibitory avoidance tasks (Liang, Bennett and McGaugh, 1985) as well as discrimination tasks where choice rather than response latency is used to assess retention. For example, in a recent study we found that posttraining epinephrine alters subsequent long-term retention of a footshock-motivated visual discrimination task (Introini-Collison and McGaugh, 1986). Further, while the effects of epinephrine on memory have been typically studied in experiments using aversive motivation, we have found that epinephrine can also influence the retention of an appetitively-motivated discrimination task. In both appetitively and aversively motivated training tasks, the effects of epinephrine on retention are blocked by systemically administered α- and β-antagonists. (Sternberg et al., 1985; Sternberg et

al., 1986). Our findings indicating that epinephrine has highly similar effects in a variety of learning tasks using different motivation and different response measures are consistent with the view that epinephrine has a general role in the modulation of memory storage.

Effects of Opiate Receptor Agonists and Antagonists

There is also extensive evidence that memory, as assessed in a variety of types of training tasks, including aversively-motivated tasks as well as appetitively-motivated tasks, can be modulated by posttraining treatments affecting opiate receptors. Retention is generally impaired by posttraining administration of opiate receptor agonists (e.g. morphine, β-endorphin) and enhanced by opiate receptor antagonists such as naloxone and naltrexone. The memory-enhancing effects of opiate receptor antagonists appear to be based on central effects, since retention is not affected by posttraining i.p. administration of naltrexone methyl bromide (MR2263), an opiate receptor antagonist that does not readily pass the blood-brain barrier. Further, the memory impairing effects of β-endorphin as well as morphine also appear to be centrally mediated since MR2263 does not antagonize the effects of these treatments (Introini, McGaugh, and Baratti, 1985) .

Interaction of Adrenergic, Noradrenergic and Opiate Systems

Evidence from several studies suggests that epinephrine effects on retention may involve interactions with a brain opioid peptide system. For example, the findings that the memory-impairing effect of high doses of epinephrine is blocked by naloxone (Introini-Collison and McGaugh, 1987) are consistent with other evidence indicating that epinephrine releases brain β-endorphin. However, the finding that low doses of epinephrine block the memory-impairment produced by posttraining β-endorphin (Introini-Collison and McGaugh, 1987) clearly indicates that the memory-enhancing effects of low doses of epinephrine do not involve the release of β-endorphin. Further, we have found that low doses of naloxone and epinephrine which do not affect memory when administered alone significantly enhance memory when administered together (Introini-Collison and McGaugh, 1987). As is discussed below, such an additive effect is expected in view of evidence suggesting that the memory-modulating effect of both of these treatments involves the release of central norepinephrine (NE). Another way to examine the interaction of epinephrine with opioid peptides is to use animals that have received a novel experience prior to training. Under such conditions, brain β-endorphin has been shown to be reduced for several hours. In animals given a novel experience prior to training, posttraining injections of naloxone do not affect retention, and retention is enhanced, rather than impaired, by high doses of epinephrine (Izquierdo and McGaugh, 1985; Izquierdo and McGaugh, 1987). Such findings provide additional evidence that retention is modulated by posttraining release of β-endorphin and that the effects of low and high doses of epinephrine on memory involve different mechanisms.

Involvement of the Amygdala

Findings of other recent studies from our laboratory suggest that effects of naloxone and epinephrine on memory may involve the activation of NE receptors within the amygdala. Extensive anatomical evidence suggests that

the amygdaloid complex is a likely candidate for a locus of the effects of treatments affecting opiate and noradrenergic receptors. Noradrenergic receptors are found in several amygdala nuclei particularly in the central and basolateral nuclei, and opiate receptors are also found throughout the amygdaloid complex. The view that epinephrine affects memory through influences involving the amygdala is supported by the finding that lesions of the stria terminalis (ST), a major amygdala pathway, block the memory-enhancing effects of posttraining peripheral injections of epinephrine and naloxone as well as the memory-impairing effects of β-endorphin (Liang and McGaugh, 1983; McGaugh, Introini-Collison, Juler, and Izquierdo, 1986).

Involvement of Intra-amygdala Norepinephrine

While it is generally assumed that epinephrine does not pass the blood-brain barrier, the route by which epinephrine affects the brain is not yet known. One possibility is that the effects of peripheral epinephrine may be mediated by activation of visceral afferents projecting to central noradrenergic systems which are known to project to the amygdala (via the ST and the ventral amygdalo-fugal pathway). If modulation of memory storage processes involves noradrenergic activation within the amygdala, then it should be possible to influence retention with posttraining intra-amygdala injections of noradrenergic agonists and antagonists. There is extensive evidence to support this implication. Studies from our laboratory have shown that retention is enhanced by low doses of NE administered intra-amygdally posttraining (Liang, Juler and McGaugh, 1986). The effect of NE was blocked by concurrent intra-amygdala injections of propranolol. Further, posttraining intra-amygdala injections of propranolol blocked the retention-enhancing effects of peripherally administered epinephrine. This finding provides strong evidence for our view that epinephrine affects memory by influencing the release of NE within the amygdala.

Interaction of Noradrenergic and Opiate Systems

Other recent findings from our laboratory support the view that the modulating effects of naloxone on retention may involve activation of noradrenergic receptors within the amygdala (McGaugh, Introini-Collison, and Nagahara, 1988). Rats in these experiments received immediate posttraining intra-amygdala injections of α- and β-adrenergic blockers or a buffer control solution, through implanted cannulae, followed by i.p. injections of naloxone. The experiments examined the effects of these treatments on 1-week retention of an inhibitory avoidance task as well as Y-maze discrimination. In both tasks, the memory enhancing effect of posttraining naloxone was blocked by propranolol (a $\beta_{1,2}$ antagonist), atenolol (a β_1 antagonist) and zinterol (a β_2 antagonist), in doses that did not affect retention when administered alone. However, the α-antagonists prazosin and yohimbine did not block the effect of naloxone. Moreover, propranolol injected into either the cortex or caudate nucleus immediately above the amygdala injection site did not block the memory-enhancing effects of naloxone. We have interpreted these findings as indicating that peripherally-administered naloxone influences memory by blocking opioid peptide receptors located within the amygdaloid complex. Thus, on the assumption, for which there is extensive evidence, that opioid peptides inhibit the release of NE, systemically-injected naloxone would be expected to induce the release of NE within the amygdala.

Overall, our findings fit well with other evidence indicating that the amygdala is involved in the storage of recently acquired information. We have not as yet determined how activation of NE receptors within the amygdala influences retention. In view of evidence that lesions of the amygdala do not impair the retention of long-term memory, it seems likely that the amygdala modulates storage in other brain regions. Alternatively, the amygdala might serve as a temporary storage site. Our findings indicating that lesions of the stria terminalis block the memory-modulating effects of a variety of posttraining treatments, including brain stimulation, epinephrine, naloxone and β-endorphin, seem most consistent with the view that the amygdala is part of a system which serves to modulate memory storage at sites in other brain regions.

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NORMAN M. WEINBERGER
RAPIDLY ACQUIRED MEMORY IN SENSORY CORTEX

Contemporary brain-behavior formulations are based largely on conceptualizations whose experimental origins may be traced to the 19th century. Chief among these is that the functional organization of the vertebrate brain is fundamentally an extension of the functional organization of the spinal cord. At the neocortex, this became sensory, motor, and "association" cortex. In this plan, sensory cortex is considered to be the highest level of pure sensory analysis, i.e., a reflection of the stimulus-produced state of the relevant sensory receptor cells.

It has become apparent that this schema is wrong. A basis for understanding information encoding and storage in the neocortex requires an appreciation of the fact that this structure is enormously dynamic, and that plasticity is a property of cortical tissue which is expressed in sensory cortex throughout the life span of organisms. Evidence comes from three areas: development, recovery of function, and learning.

With respect to development, the response properties of visual cortex neurons depend critically upon the type of early visual experience (e.g., Weisel and Hubel, 1966). Plasticity of this type is generally limited to the first several months of life (e.g., Sherman and Spear, 1982).

Regarding recovery of function, receptive fields in somatosensory cortex reorganize following insult to the peripheral somatosensory system. Thus, the absence of input from a digit results, not in a functional lacuna within its former projection region of areas 3b and 1, but in a "takeover" of that region by inputs from neighboring skin. These effects occur in adult animals and may be fully expressed in several weeks (e.g., Merzenich et al., 1983, 1984; Wall and Cusick, 1984).

It might be argued that plasticity during development and following injury are still compatible with the view that sensory cortex has a pure sensory function. However, extensive, systematic experiments in learning have shown conclusively that sensory cortex is not only plastic, but that such plasticity is rapidly expressed during learning. Hundreds of studies have reported that the responses of sensory cortex to environmental stimuli

change systematically when the signal value of those stimuli is altered by associative processes. Although demonstrated for all sensory systems and several training situations, the most extensive documentation is for classical conditioning and the auditory cortex. A detailed account of this field was prepared as part of the contract (Weinberger and Diamond, Progress in Neurobiology, 1987).

These findings, by themselves, do not directly address the critical issues involved in information processing and encoding. Thus, learning-induced sensory cortical plasticity could reflect either (1) a general change in cortical responsivity or (2) a specific change in the way that information is processed by sensory cortex. Direct tests of these alternatives have been attempted, and it has been claimed that the results support the "general change" hypothesis. Detailed critiques of these claims have been presented elsewhere (Weinberger and Diamond, in press); for present purposes, it is sufficient to note that the findings are inconclusive due, in part, to the absence of controls for non-associative factors.

In order to resolve this issue, it is insufficient to test learning effects on neuronal responses to a single stimulus, as done in previous studies. Rather, it is necessary to determine the effects of learning on the processing of a stimulus dimension. Under this contract, we have combined sensory physiology and learning paradigms within the same experiment. As described below, the results in both cats and guinea pigs for both habituation and classical conditioning demonstrate that the "processing specificity" theory is correct. In other words, the encoding of stimuli whose significance is acquired by experience is accomplished by retuning the receptive fields of single neurons.

Previous Findings

Previous relevant findings from my laboratory are summarized briefly here.

In order to determine if the actual neurophysiological encoding of stimuli is altered by its acquired signal value, we first had to develop a behavioral preparation in which (a) the stimulus is controlled at the receptor level, (b) sensory feedback from learned responses cannot influence the relevant neuronal activity, (c) validation of acquired signal value is provided behaviorally, and (d) sensory neuronal responses can be recorded without artifact continually during the acquisition phase of learning. All of these criteria were satisfied by recording the pupillary dilation conditioned response in cats under neuromuscular blockade. This CR exhibits all of the major features of other classically conditioned responses. These include acquisition, extinction, discrimination both within and between modalities, discrimination reversal, conditioned inhibition, inhibition of delay, and also habituation and dishabituation (Ashe et al., 1976; Cooper, Ashe, & Weinberger, 1978; Oleson, Westenberg, & Weinberger, 1972; Oleson, Vododnick, & Weinberger, 1973; Oleson, Ashe, & Weinberger, 1975; Ryugo & Weinberger, 1978; Weinberger, Oleson, & Haste, 1973; Weinberger, Oleson, & Ashe, 1975).

Of particular interest and advantage is the finding that acquisition is extremely rapid, consistent CRs being present in 5-10 trials and asymptote in 20-30 trials. This is sufficiently rapid to permit simultaneous record-

ing of single neuron's discharges during acquisition, even after a preceding sensitization control phase.

Following behavioral experiments which established that pupillary conditioning obeys the same descriptive laws as somatic conditioned responses, we performed studies in which neurophysiological responses to acoustic conditioned stimuli were recorded at various levels of the auditory system during conditioning. The salient findings are listed below.

The receptor potential (cochlear microphonic) is unaffected by learning (Ashe et al., 1976).

Primary auditory cortex rapidly develops discharge plasticity to the conditioned stimulus during simple acquisition, two-tone discrimination, and discrimination reversal (Oleson et al., 1975; Weinberger, 1984; Weinberger et al., 1984a,b).

The obligatory thalamic gateway to the auditory cortex contains morphologically-distinct nuclei in which two functions are compartmentalized; the lemniscal, ventral medial geniculate nucleus (MGv) accurately reflects the physical parameters of sound but is unaffected by learning like the receptor potential; in contrast, the magnocellular medial geniculate nucleus (MGm) is not tonotopic but rapidly develops physiological plasticity during learning (Ryugo and Weinberger, 1978; Weinberger, 1982a). The MGm is unique in that it alone projects to <u>all</u> six cortical auditory fields.

Local synaptic plasticity develops in the MGm (but not the MGv), as evidenced by long-term potentiation at the levels of both population responses (Gerren and Weinberger, 1983) and single neurons (Weinberger, 1982b).

All early studies in which so-called "cluster" or multi-unit recordings were employed were extended to single unit studies in which only one cell was recorded during an entire training session (Weinberger, 1982a; Weinberger et al., 1984; Diamond and Weinberger, 1984). Previous findings were replicated and extended to reveal that "cluster" recordings mask important details of discharge plasticity which can be observed only at the level of single neurons (Weinberger, 1982a; Weinberger et al., 1984).

<u>Research Progress under the Current Contract</u>

Classical Conditioning

A re-examination of classical conditioning has revealed that it is not "simple," as previously thought. Thus, Pavlovian conditioning involves far more than the acquisition of a single, experimenter-designated somatic motor response. In fact, several conditioned responses develop rapidly prior to the emergence of the designated somatic conditioned response.

Supported by the current contract, we recently completed a survey of the conditioning literature spanning the past fifty years (Lennartz and Weinberger, in preparation). The most salient result was that there is a basic dichotomy in learning rates for response systems employed in both animal and human defensive classical conditioning. This is summarized in Appendix B which shows that autonomic responses and conditioned suppression (which

itself may be an indirect measure of autonomic conditioning) develop conditioned responses rapidly (i.e., 5-10 trials). In contrast, nictitating membrane, eyelid retraction, and limb or tail flexion require 60-90 trials. The difference between the former and latter groups of responses is statistically significant ($p<.001$). Other variables (e.g., stimulus intensity, inter-stimulus intervals, etc.) did not differ significantly, so the differences in learning rate are attributable to response system per se.

This behavioral dichotomy is consistent with the view that classical conditioning involves at least two stages: (1) a rapidly-developing stage in which animals learn that the conditioned stimulus predicts the unconditioned stimulus; this is detected behaviorally as the rapid, simultaneous development of autonomic conditioned responses; (2) a slowly-developing stage in which animals learn to make a single somatic response in anticipation of the delivery of a noxious stimulus, e.g., eyeblink for air puff to the eye or flexion for shock to a limb. Accordingly, neural correlates of "learning" must be examined within this extended framework.

Classical Conditioning Rapidly Induces Specific Plasticity of Frequency Receptive Fields

The first step in solving the problem of the functional role of discharge plasticity in sensory cortex during learning was achieved by combining techniques from sensory physiology and the neurophysiology of learning; the findings revealed that such plasticity in the secondary (AII) and ventral ectosylvian (VE) auditory fields actually reflects a highly specific change in the frequency receptive fields of single neurons -- the greatest effect is at the frequency of the conditioned stimulus. The receptive fields are stable in the absence of conditioning, and the changes in receptive fields are maintained unless the behavioral learning is altered by extinction, in which case they revert to pre-conditioning status. These effects were found for both narrowly and broadly-tuned cells (Diamond and Weinberger, 1986; Weinberger and Diamond 1987, in press).

The Role of Context in the Expression of Learning-Induced Physiological Plasticity in Auditory Cortex

An exhaustive comparison of the characteristics of the <u>expression</u> of plasticity was undertaken and completed. For every neuron, the nature of the associatively-induced plasticity change in response to the CS frequency was compared under two contexts: during training trials, i.e., pairing of the CS and US and during determination of frequency response functions. In each case, the development of plasticity was determined with reference to appropriate control periods and procedures, e.g., sensitization period for conditioning and pre-conditioning period for frequency receptive fields. We found that the expression of plasticity was context-dependent; i.e., responses to the CS during pairing might increase while responses to the same tone during FRF determination might decrease (Diamond and Weinberger, 1988, in press).

These findings provided the impetus to develop a theoretical schema for neuroplasticity and learning, which we termed the <u>Functional Mosaic</u>. As explained in great detail elsewhere (Diamond and Weinberger, submitted), each neuron is viewed as embedded within a mosaic of influences. We distin-

guish the induction of plasticity during learning from the expression of such plasticity. Combinatorial analysis indicated that the effects of context could alter the expression of plasticity which had been induced during conditioning. This formulation implies that learning does not produce alterations in specific circuits independent of the context. Rather, context, i.e., the external and internal sensory milieu, constitutes part of the mosaic of influences upon each neuron. This is a more dynamic view of the neurophysiological view of learning than is currently prevalent.

On-Line Simultaneous Recording of Discharges from Neighboring Neurons

In order to permit future studies to (1) obtain data from large numbers of single neurons easily, (2) obtain data simultaneously from neighboring neurons, and (3) record from the same single neurons over a period of days rather than hours, we have recently developed a computer-based method for extracting single unit data from multiple-unit recordings in animals bearing chronically indwelling microelectrodes. The technique also provides on-line histograms and wave-form sorting for which strict statistical confidence limits can be specified (Cassady, Diamond and Weinberger, in preparation).

Chronic Single Unit Recording from Auditory Cortex over Days

Assessment of retention of neuronal plasticity is an important, but unrealized, goal of neuronal studies of learning. In order to achieve that goal, we have devised an array of chronic microelectrodes from which recordings of the same waveforms can be obtain over a period of many hours, usually a few days, and in some cases almost two weeks (Condon, Diamond and Weinberger, in preparation).

Chronically Prepared Guinea Pig for Analysis of Learning in the Auditory System

Because of the need for acoustic control, it is necessary to restrain animals so that the speaker is fixed with reference to the tympanic membrane. We found this could be accomplished without drugs in the waking guinea pig by developing a non-traumatic restraining hammock and head holder (Condon, Chin, Lennartz and Weinberger, in preparation).

Frequency Specific Plasticity During Habituation in the Guinea Pig

We employed the techniques described above to determine whether learning in the form of habituation also induced frequency-specific plasticity in the tuning of neurons. Following determination of tuning curves, a single tone frequency was repeated several hundred times. Response decrements in both clusters of neurons and single cells extracted from clusters were obtained. Post habituation tuning curves showed that a frequency specific decrement centered on the frequency of the repeated stimulus (Condon and Weinberger, in preparation). Therefore habituation does not cause a general alteration of neuronal excitability, and experience-dependent retuning of frequency receptive fields is not limited to classical conditioning or to the cat auditory cortex.

Frequency Specific Changes in Receptive Fields: Time Course in Guinea Pigs

Employing the techniques developed for the guinea pig, subjects underwent two-tone discriminated classical conditioning over a 2-3 day period. Recordings of unit clusters and single neurons extracted from clusters revealed frequency specific changes in tuning curves. Furthermore, retention was obtained 24-48 hours after initial training. These findings show that the effects of learning upon tuning curves are not transient and are not limited to simple conditioning in the cat.

Frequency-Specific Plasticity in the Anesthetized Guinea Pig Following Learning

One method of determining the encoding of neuronal memories is to seek their representations at a time when no new learning is possible. Accordingly, we conditioned guinea pigs while awake and then placed them under deep general anesthesia. Recording from the magnocellular medial geniculate nucleus before and after behavioral conditioning, we found that learning produced a frequency-specific change in tuning of neuronal clusters (Lennartz, Bourg and Weinberger). This provides the first evidence that learning produces physiological plasticity that is sufficiently robust to be "read out" under subsequent anesthesia.

Facilitated Discriminative Avoidance Behavior in the Guinea Pig

In order to extend the domain of generality of tuning curve changes, we have trained guinea pigs in an instrumental avoidance situation to complement work in classical conditioning. Guinea pigs were trained in a Brogden wheel using two tones and CS durations of 10 sec. We were able to facilitate two-tone discrimination by reducing responding to the CS- using a response-contingent paradigm. Briefly, response during the CS+ produced termination of the stimulus and avoidance of shock. Responses to the CS- produced another CS-(10 sec.) until animals no longer responded during this stimulus. In contrast to a control group (non-contingent), the experimental group exhibited superior discriminative performance (Bakin, Bourg and Weinberger, in preparation).

Facilitated Two-Tone Discrimination and Discrimination Reversal

In order to determine the extent to which the neuronal findings generalize to a different motivational situation and to the normal state lacking neuromuscular blockade, we extended pupillary conditioning to undrugged animals bearing indwelling stimulating electrodes in "rewarding" areas of the hypothalamus. Behavioral verification of the rewarding nature of hypothalamic stimulation was obtained, together with rapid pupillary conditioning, discrimination and discrimination reversal between two tones. Most remarkably, all of these behavioral effects were obtained within a single training session (Schweitzer, Diamond and Weinberger, 1986). We also were able to obtain stable tuning curves for single neurons in auditory cortex. Combined learning studies have not yet been undertaken.

Sensitivity of Auditory Cortical Neurons to Tonal Contour

During the course of obtaining tuning curves, we noted that neuronal responses might be dependent to some extent upon whether frequencies were presented in ascending or descending order. We therefore studied the responses of single neurons in the cat to differing tonal "contours". Indeed, neurons were highly sensitive to parameters of tone sequences (five tones), including frequency direction. These findings show that determination of receptive fields may be contextually dependent (Weinberger and McKenna, in press).

Modeling of Modulation of Excitability of Auditory Cortical Neurons

Given the known architecture of the thalamocortical auditory system and the differential plasticity of the medial geniculate nucleus, it became possible to investigate how pyramidal neurons of auditory cortex may undergo modulation of excitability. A realistic model of such neurons was implemented using the techniques developed by D.H. Perkel. We found that input to distal dendrites could greatly increase excitability, depending upon the relative time of arrival of such "non-specific" input with respect to sensory-specific input (McKenna, Perkel and Weinberger, in preparation).

Conclusions

Central to mechanisms of learning and memory, as expressed in the mammalian brain, are the cerebral neocortex and association. Our continuing line of inquiry, is based on a synthesis of these two research fields with sensory neurophysiology. The major result of research under the present contract is the discovery that the specific encoding of information in behaving animals is accomplished in auditory neocortex, not by feature extraction but by the operation of active learning processes. This dynamic characteristic of information storage encoding implies that the functional organization of information in sensory cortex comprises an adaptively-constituted information base.

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GARY LYNCH
MECHANISMS OF LEARNING AND MEMORY IN CORTICAL NETWORKS

The research program sought to test for linkages between long-term potentiation (LTP) and learning and memory. Three approaches were followed:

1. Test for the effects of drugs that block LTP on learning and memory;

2. Use electrical stimulation as a behavioral cue and test if LTP occurs in concert with learning;

3. Develop computer simulations that incorporate synaptic "learning rules" based on LTP and test if recognizable forms of learning emerge.

Collaborative relationships with J. McGaugh's group were required for the first goal and with R. Granger for the third project.

Pharmacological Studies of Learning and Memory

For a variety of reasons described in the original proposal (also see Lynch and Baudry, 1984) we had hypothesized that LTP, at least as the effect is understood from studies of hippocampus, is predominantly a telencephalic phenomenon. This idea received unexpected support from the discoveries that N-methyl-D-aspartate receptors are concentrated in telencephalon and are essential to LTP induction.

Therefore, to study the role of LTP in behavior it was necessary for us to identify learning and memory tasks that involve networks running through cortex, hippocampus, and other telencephalic structures. At the same time, we sought behavioral paradigms that could be related to recognizable aspects of human memory processing. These constraints caused us to concentrate our behavioral work on the olfactory system, the first, second, and third stages of which are telencephalic; moreover, the olfactory system is much more directly linked than are the modalities to hippocampal and frontal cortical systems thought to be crucial to human memory encoding.

We have established that olfactory memory in rats bears a number of similarities to what cognitive psychologists sometimes refer to as "data" memory (Staubli et al., 1987, for a paper describing experiments carried out over the course of the project). Moreover, lesions that separate olfactory cortex from hippocampus produce an anterograde amnesia syndrome that is strikingly like the "rapid forgetting" deficit reported for humans with temporal lobe and hippocampal damage. Thus the rats learn to discriminate between novel odor cues but show no retention when tested one hour later (Staubli et al., 1986); also like human amnestics the rats do retain memories (for discriminations) learned well in advance of brain damage (Staubli et al., 1987). It might be noted that these results provided the first rat model of a characteristic form of human memory dysfunction.

Two classes of drugs have been identified which selectively block hippocampal LTP: antagonists of N-methyl-D-aspartate receptors (Collingridge et al., 1983; and many others) and inhibitors of calpain, a calcium activated protease (Staubli et al., 1987). In collaboration with Richard Morris (Edinburgh University, Scotland) we found that an NMDA antagonist (D-AP5), infused at concentrations that prevented LTP, blocked spatial learning (Morris et al., 1986); similar effects were obtained with leupeptin, a calpain inhibitor (Staubli et al., 1985). Leupeptin and the NMDA antagonist also prevent the encoding of memory in our olfactory discrimination task (Staubli et al., 1985, 1988).

What of memory tasks that are not so dependent upon hippocampus and cortex? Visual discrimination learning and shock avoidance learning are such tasks and we have found that these problems are not disturbed by either leupeptin or D-AP5 (Staubli et al., 1985; Morris et al., 1986). Avoidance conditioning is reported by a number of investigators to be blocked by anisomycin, a protein synthesis inhibitor. Again working with McGaugh's group, we found that this drug does profoundly interrupt both active and passive avoidance but at the same dosages does not disrupt olfactory or spatial learning. We have thus arrived at a pharmacological double dissociation suggesting that different forms of memory are dependent upon different cellular chemistries (see Staubli et al., 1985); moreover, we have provided evidence for the idea that the mechanisms responsible for LTP are involved in those forms of memory that involve telencephalic circuitries.

Electrical Stimulation as a Behavioral Cue

If LTP were to be involved in memory encoding, then patterns of electrical activity that result in behavioral learning in forebrain would be expected to produce LTP-like effects. We tested this idea again using the olfactory discrimination paradigm. The olfactory nerve travels from the nasal receptors to the olfactory bulb located underneath the frontal lobes; the bulb in turn projects via the lateral olfactory tract (LOT) to the olfactory (piriform-entorhinal) cortex. The LOT projections exhibit very little topography; i.e., they distribute themselves in a quasi-random fashion across the outer layers of cortex. This suggests that activity in <u>any</u> subgroup of LOT fibers could potentially carry information denoting the presence of a particular odor. Rats sniff (sample) odors 3-5 times per second (Macrides et al., 1983; Eichenbaum et al., 1987). Accordingly, we stimulated the LOT with a permanently implanted electrode at 5/sec with short bursts of activity and asked if the animals would behave as though an odor were present in an olfactory discrimination problem. This proved to be the case: the rats responded to electric odors much as they did to actual odors and learned quickly to discriminate them from real odors or from other electric odors. Retention of the electric odors was also excellent when tested several days later. Chronic recording electrodes revealed that learning was accompanied by long-term potentiation of the LOT-olfactory cortex synapses. Interestingly enough, the same stimulation patterns applied outside the learning situation do <u>not</u> induce LTP (Roman et al., 1986). These experiments indicate LTP does occur with behaviorally relevant, albeit artificial, cues and that it exhibits an unexpected situational dependency in layer II olfactory cortex.

Computer Simulations of LTP-based Learning Rules

The third project sought to answer the following question: what types of network level effects emerge when the physiological rules that determine when LTP is induced are implemented into a computer simulation of the superficial layers of olfactory cortex. Experimental work in the laboratory led to the discovery of a set of LTP rules. Specifically, it was found that two characteristic features of hippocampal physiology - short firing bursts by individual cells and the 4-7 Hz theta rhythm -when combined into an electrical stimulation paradigm prove to be ideal for producing LTP (Larson et al., 1986). Subsequent work led to two further findings: 1) the mechanisms by which theta bursting activates the triggers for LTP (Larson and Lynch, 1988) and 2) a set of rules describing how spatial and temporal convergences by inputs affect the degree of LTP experienced by a given input (Larson and Lynch, 1986; Larson and Lynch, 1988). This collection of findings was then formulated as a set of algorithms to use in the network model.

A series of ever more biologically accurate simulations of layers I and II of cortex have been constructed with the most recent model using 200-500 cells and 100 LOT input lines. The network also has local inhibitory interneurons, feedback lines, and incorporates a sizeable number of physiological rules in addition to LTP (e.g., probabilistic transmitter release, three forms of inhibition). Input signals are modelled after those used in

the electric odor experiments with a given cue ("odor") using about 20% of all input lines.

A very satisfying result from this work was the observation that the various physiological rules operate smoothly together. After learning a significant number of cues (10-30) the network produces different responses on successive samples of the same cue (i.e., at successive samples with a 200 msec interval between them). The first response was common to several cues that shared a significant number of components in common; later responses were specific to individual stimuli in that group. These LTP rules coupled with the repetitive sampling mode that characterizes olfaction (and the other sensory modalities) produce two seemingly contradictory functions: 1) a category response (on the first sniff) that signifies the presence of any member of a learned group, including cues that have not been previously experienced and 2) orthogonalization of inputs (on later sniffs) such that very similar members of a group produce very different output responses (Lynch and Granger, 1988; Lynch et al., 1988b; Granger et al., 1988).

Cognitive psychologists have shown that this type of hierarchical information storage and readout is common to many human perceptual operations; e.g., an observer noting the presence of an animal sitting on a tree limb will report first that it's a bird and second that it's a robin. Our results indicate that this mode of functioning reflects fundamental properties inherent in the learning rules and designs of a particular type of cortical network.

Conclusions

1. It is likely that there are at least two quite different chemical systems involved in memory, one that is blocked by protein synthesis inhibitors and a second that is sensitive to drugs that block long-term potentiation.
2. Synaptic plasticity of the LTP type appears to be involved in those forms of memory that are dependent upon telencephalic networks.
3. Behavioral work indicates that one such LTP-related memory form corresponds to the "fact memory" system described by cognitive psychologists. (While we stand by this conclusion, our most recent work, including that involving computer simulations, is causing us to move away from the "fact" vs. "procedural" dichotomy; see Lynch and Baudry, 1988).
4. Computer simulations using empirically derived physiological rules and an anatomical design based on layers I and II of cortex have led to the hypothesis that synaptic plasticity of the LTP type causes hierarchical storage of information (i.e., representations for categories and representations for specific cues within those categories). We propose that successive time-locked processing steps are used to read out levels of perceptual (recognition) memory from cortical networks of this type and that this operation is ubiquitous to cortical functioning.

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RICHARD H. GRANGER
SIMULATION AND ANALYSIS OF CORTICAL CIRCUITS

We have undertaken extensive computational modeling of layer II piriform (olfactory) cortex, based on strict anatomical, physiological and biophysical attributes of layer II piriform cells, as well as on known electrical stimulation parameters of this cortical area, as derived from experiments in which animals are given direct electrical stimulation of piriform via the lateral olfactory tract (LOT), rather than olfactory input. When this stimulation mimics the intrinsic theta-burst characteristics of cells in alert animals performing olfactory discrimination learning, piriform synapses potentiate, and the animals learn behaviorally, both remembering spe-

cific electrical stimulations and learning (in less than 5 trials) to distinguish between two different such stimulations or 'electric odors' (Staubli et al., 1987; Staubli and Lynch, 1988). Using this paradigm, we have modeled what we believe to be the biological mechanisms directly underlying this specific form of olfactory learning.

In contrast to most forms of associative learning (such as classical conditioning) which may require dozens to hundreds of trials, there are forms of human learning characterized by extremely rapid acquisition, long retention, and enormous capacity: for instance, Standing (1973) found that 10,000 photographs, each displayed to subjects just once, for only seconds, were learned to 90% criterion by subjects; this ability to incrementally learn large numbers of minimally salient stimuli with very little exposure and no opportunity for rehearsal, may be characteristic of human "everyday learning," i.e., the apparently effortless acquisition and retention of enormous numbers of minute-to-minute environmental cues. In the olfactory learning task we have studied, animal subjects learn rapidly, incrementally and with long retention and large capacity (Staubli et al., 1987). Physiological and anatomical experimentation has identified the brain structures underlying these learning and memory abilities, and has yielded data that enables accurate biological simulation of the normal operation of these structures in response to the inputs they receive during this type of learning. The resulting simulations of layer II sensory cortex (piriform cortex) empirically reproduce important aspects of the behavioral data, as well as yielding to analytical treatment (Lynch and Granger, 1988). As a result, we have been able to construct a mechanism that incrementally generates unique encodings of large numbers of input stimuli in a small number of learning trials, with large capacity. Most 'neurally-inspired' networks have limited capacity, require large numbers of learning trials, and learn nonincrementally, i.e., they require all items that are to be learned to be available at once, in advance of any testing -- if stimuli are instead presented one at a time, as in actual experience, early items tend to be lost as subsequent ones are learned, and there will be interference among learned items. Our biological network differs strikingly from abstract 'neurally-inspired' networks in its learning and performance rules, which arise from the different rise times, intensities and durations of a set of three distinct inhibitory currents present in the network (and the model): short IPSPs, long hyperpolarization (LHP), and extremely long cell-specific afterhyperpolarization (AHP). The integrative action of these and other physiological properties, embedded in the anatomical architecture of this cortical structure, enable this single-layer threshold network to use timing rules to extract and encode multiple levels of hierarchical information about each stimulus, rather than simply generating a single representation of a cue as do virtually all current abstract networks.

In particular, probabilistic quantal transmitter-release properties of piriform synapses give rise to probabilistic postsynaptic voltage levels which, in combination with the activity of local patches of inhibitory interneurons, differentially select or 'recruit' rostral layer II piriform cells, depending on the relative innervation of these cells by the lateral olfactory tract (LOT). Time-locked firing to the theta rhythm (Larson and Lynch, 1986) enables distinct spatial patterns to be read out against a relatively quiescent background firing rate. Training trials using the physiological rules for induction of long-term potentiation (LTP) enhance

both the conductances and the quantal release characteristics of active synapses, yielding stable layer-II-cell spatial firing patterns for learned cues. Multiple simulated olfactory input patterns (i.e., those that share many chemical features) will give rise to strongly-overlapping bulb firing patterns, activating many shared lateral olfactory tract (LOT) axons innervating layer Ia of piriform cortex, which in turn yields highly overlapping layer-II-cell excitatory potentials, enabling this spatial layer-II-cell encoding to preserve the overlap (similarity) among similar inputs. At the same time, those synapses that are enhanced by the learning process cause stronger cell firing, yielding strong, cell-specific afterhyperpolarizing (AHP) currents. Local inhibitory interneurons effectively select alternate cells to fire once strongly-firing cells have undergone AHP. These alternate cells then activate their caudally-flowing recurrent collaterals, activating distinct populations of synapses in caudal layer Ib. Potentiation of these synapses in combination with those of still-active LOT axons selectively recruit the response of caudal cells that tend to enhance the differences among even very similar cues.

Empirical tests of the computer simulation have shown that, after training, the initial spatial layer II cell firing responses to similar cues enhance the similarity of the cues, such that the overlap in response is equal to or greater than the overlap in input cell firing (in the bulb): e.g., two cues that overlap by 65% give rise to response patterns that overlap by 80% or more. Reciprocally, later cell firing patterns (after AHP), increasingly enhance the differences among even very similar patterns, so that cues with 90% input overlap give rise to output responses that overlap by less than 10%. This difference-enhancing response can be measured with respect to its acuity; since 90% input overlaps are reduced to near zero response overlaps, it enables the structure to distinguish between even very similar cues. On the other hand, the similarity-enhancing response is properly viewed as a partitioning mechanism, mapping quite-distinct input cues onto nearly-identical response patterns (or category indicators). Using a statistical metric for the information value of categorizations, we have measured the value of partitionings produced by the piriform simulation network.

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